DECLARATION UNDER 37 C.F.R. § 1.132

08 November 2004

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, **MATHIAS WALTHER**, a citizen of GERMANY, of Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, England., hereby declare:

1. I received a Diplom in Chemistry from the Albert-Ludwigs Universitaet in Freiburg in 1993. I received a Ph.D. degree in Polymer Sciences from the Albert-Ludwigs Universitaet in Freiburg in 1996. I carried out post-doctoral studies at the Melville Laboratory (Cambridge, UK) from 1996 to 1998.

2. I joined Pfizer Global Research and Development in 1998 as a Scientist. Since that time, I have carried out research in the area of formulation development of modified release dosage forms.

3. I commissioned a series of experiments which were carried out by Prof. Dr. Roland Bodmeier (Freie Universitaet Berlin, Germany). The object of these experiments was to assess whether a pharmaceutical composition made in accordance with the teaching of Jackson et al (WO-A-00/06161), which incorporates the teaching of Stevens et al (US-B-5,112,621), gives a sigmoidal pattern of drug release. To this end, the composition described in Stevens (column 2, lines 61-67) was adapted by replacing diltiazem hydrochloride with eletriptan hemisulphate.

4. The following materials were used in the experiments.

Ingredient	Function	Supplier
Eletriptan hemisulfate	Drug	Pfizer
Sugar spheres 600-710 μm	Cores	Pfizer
Hydroxypropylmethylcellulose Methocel E3	Binder	Colorcon
Talc Pharm S USP	Antisticking agent	Lucenac
Ethylcelllose Ethocel N 22 NF	Release rate modifier	Hercules
Eudragit RS	Release rate modifier	Röhm
Acetylated monoglyceride	Plasticizer	Quest

PAGE 14/19 * RCVD AT 2/22/2005 4:24:59 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:7346222928 * DURATION (mm-ss):05-46

Myvacet 9-45		
Na carboxymethylcellulose Cekol 30	Binder	Noviant

5. An attempt was made to manufacture drug-containing microparticles using extrusion/spheronisation, as recommended by US-5,112,621 (column 2, line 42). The following ingredients were used:

Ingredient	Type	Amount, g	Amount, %
Eletriptan hemisulphate	Drug	120	80
Microcrystalline cellulose	Avicel PH 101	30	20
Na carboxymethylcellulose*	Cekol 30	q.s.	q.s.

* used as 5 % w/v aqueous solution (granulation fluid)

However, using eletriptan hemisulphate rather than diltiazem, it was not possible to prepare pellets by extrusion/spheronization. Therefore, drug cores were manufactured by layering onto sugar spheres.

6. Methocel E 3 (30.3g) was dispersed in warm purified water (1299.9g, 60°C) using a magnetic stirrer until no lumps were visible. The mixture was cooled to room temperature (using ice water) with stirring until a clear solution was obtained. Eletriptan hemisulfate (403.0g) was added to the solution and stirring was continued until a clear solution was obtained. Talc (86.7g) was added and dispersed in the solution by stirring until no lumps were visible.

Sugar spheres (400g) were layered with the above dispersion under the following conditions:

Equipment	**Aeromatic STREA 1**
Inlet air temperature, °C	68
Outlet air temperature, °C	40
Airflow, m^3/h	110
Nozzle diameter, mm	1.2
Spraying pressure, bar	2
Spray rate, g/min	8.6-11.9
Drying at 40°C, min	15 min

Coating solutions for the coated sugar cores were prepared using the following ingredients:

Ingredient	Weight, g	
	Batch # El. 2.1	El. 2.2
Ethylcellulose N 22 NF	19.68	19.68
Eudragit RS	30.30	24.00
Acetylated monoglycerides Myvacet 9-45	4.32	4.32
Isopropanol	676.84	676.84
Dem. Water	75.21	75.21

PAGE 15/19 * RCVD AT 2/22/2005 4:24:59 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:7346222928 * DURATION (mm-ss):05-46

Eudragit RS, ethylcellulose and Myvacet 9-45 were dispersed in a mixture of isopropanol (676.84g) and water (75.21g) using a magnetic stirrer. The mixture was stirred overnight (> 16 h) until complete dissolution was obtained.

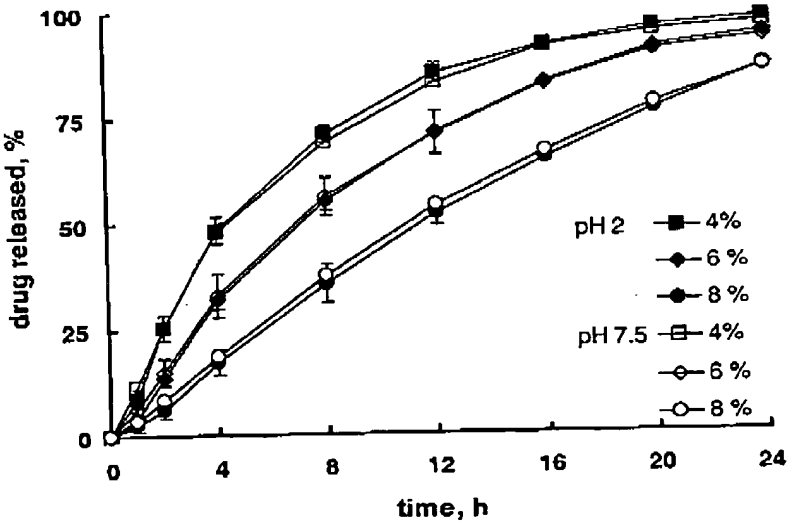
The eletriptan hemisulphate cores were coated under the following conditions at levels of 4, 6 and 8%:

Equipment	**Uniglatt lab coater**
Eletriptan layered pellets, g	400
Inlet air temperature, °C	36
Outlet air temperature, °C	30
Airflow, m^3/h	30
Nozzle diameter, mm	1.2
Spraying pressure, bar	2
Spray rate, g/min	2.9-6.8
Drying at 40°C, min	15

7. The drug release characteristics of the two batches of coated beads El. 2.1 and El. 2.2 was assessed in a USP XXIV basket apparatus (Vankel 300) at 100 rpm, 37°C at pH 7.5 (900 ml of pH 7 buffer solution) and at pH 2 (0.01 N hydrochloric acid, containing 5.23 g/l NaCl).

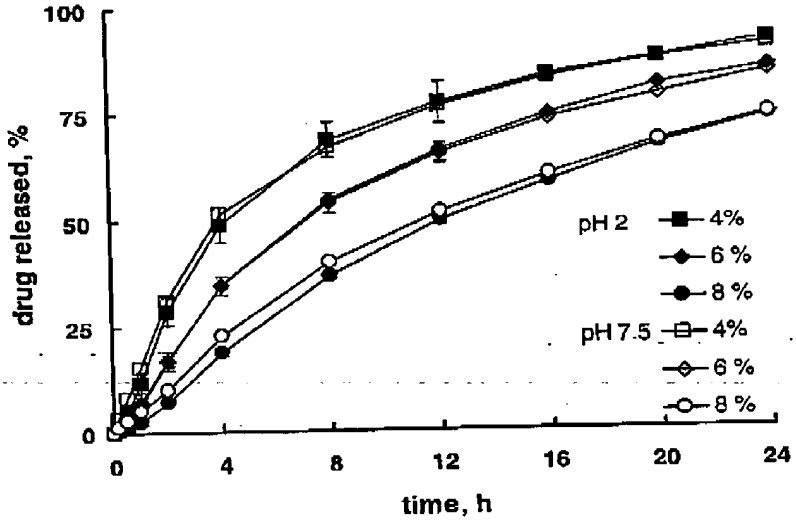
The following patterns of drug release were obtained:

El. 2.1 Eletriptan Pellets, Uniglatt
Eudragit RS/EC N 22 60:40, pH 2/pH7.5
coating level (n=3)

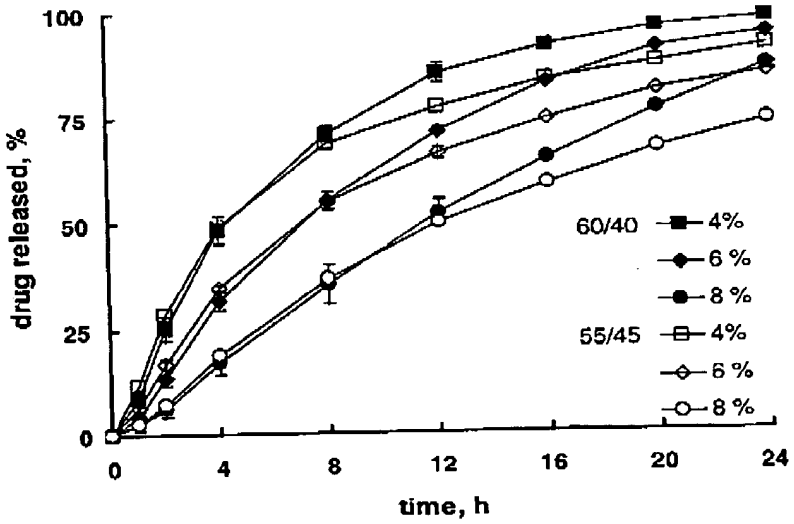


PAGE 16/19 * RCVD AT 2/22/2005 4:24:59 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:7346222928 * DURATION (mm-ss):05-46

El. 2.2. Eletriptan Pellets, Uniglatt
Eudragit RS/EC N 22 55:45, pH 2/pH 7.5
coating level (n=3)

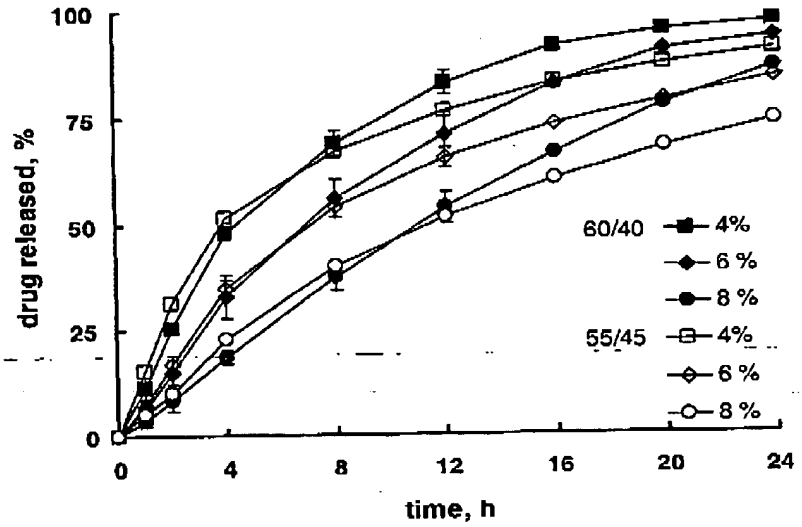


El. 2.1/El. 2.2 Eletriptan Pellets, Uniglatt
pH 2
Eudragit RS/EC N 22 ratio, coating level (n=3)



PAGE 17/19 * RCVD AT 2/22/2005 4:24:59 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:7346222928 * DURATION (mm-ss):05-46

El. 2.1/El. 2.2 Eletriptan Pellets, Uniglatt
pH 7.5
Eudragit RS/EC N 22 ratio, coating level (n=3)



8. The conclusions which may be drawn from these data are as follows:

(a) The pattern of drug release from the coated pellets was independent of pH.
(b) The drug release of pellets coated with an Eudragit RS/EC ratio of 55/45 was slightly slower than the release of beads coated with a ratio of 60/40.
(c) **The pattern of drug release was not sigmoidal.**

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that the statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code and that said willful false statements may jeopardize the validity of the application or any patent issued thereon.

08 November 2004
Date

Mathias Walther

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